Correspondence

Comments on "Trouble in Paradise"

There are statements I wish to protest in the Focus article "Trouble in Paradise" by John F. Lauerman published in *Environmental Health Perspectives* [105:914–917 (1997)]. These statements appear to have been attributed to me, but I can assure you I would never have made them.

First, there is the suggestion that I included atrazine among a list of agricultural chemicals used in pineapple cultivation. To my knowledge, atrazine was never used on pineapple fields. It does appear in Hawaiian groundwater, however, as a result of widespread use on sugar cane fields.

Second, I would never say that "none of these chemicals have been conclusively linked to adverse health effects," as the article appears to paraphrase me having said. I believe that scientific studies conclusively link all these chemicals, and still more, with harmful health effects in exposed populations. What I recall having said to Lauerman is that it is almost impossible to link, with any confidence, the cancer or other health problem of a given individual with exposure to pesticides. Thus, although a population may experience an increase in cancers or other health problems in the aggregate, the likelihood of a person with a cancer being able to prove to the satisfaction of a court of law that his or her disease was the result of exposure to a chemical is vanishingly small.

The state of Hawaii has very serious contamination problems as a result of the application of agricultural chemicals and other pesticide products. I do not wish to have my statements be interpreted in any way as minimizing this problem or my own concern for the health risks that this poses.

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Note: Atrazine was mistakenly included in the list of agricultural chemicals used in pineapple cultivation. EHP *regrets the error.*

The α2u-Globulin Discussion

One of the most valuable things to emerge from the recent series of letters published in *EHP* in connection with the proposed α2u-globulin mechanism of male rat renal carcinogenesis was the title of the final letter in the series by Melnick et al. (*1*)—"Weight of Evidence Versus Weight of Speculation to Evaluate the Hypothesis." This arresting title made me realize, for the first time, that evidence and speculation are usually irretrievably confused in the Discussion section of most papers, certainly in most of mine. It would be useful if all papers had a formal discussion of the data presented, followed by a separate section titled "Speculative Significance of the Data." When an issue assumes an importance in its own right, as with the α2u-globulin controversy, the way forward should be to list the evidence for and against the hypothesis, leading, in turn, to an estimate of its likely validity. Weak points in the hypothesis would thereby be revealed, and these could become the focus of further experiments; alternatively, the hypothesis could be abandoned. This path was not taken in the recent debate and, as a consequence, we are left with opposing speculations and no resolution.

I took part in the EPA review of the α2u-globulin mechanism referred to by several of the discussants in this debate, and most of the data recently discussed were reviewed at that time. However, the trend in that meeting was to hear the opposing arguments and to then draw a conclusion—in fact, speculations were weighed, and the balance happened to come out in favor of the probable validity of the hypothesis. What was missing from that exercise was a dissection of each of the component data sets, leading to a decision as to their individual validity. That process was started during the course of the *EHP* debate.

The α2u-globulin mechanism of renal carcinogenesis is among the richest in data and speculation of all proposed nongenotoxic mechanisms of rodent carcinogenesis. It is therefore critical that advantage is taken of the impetus provided by the recent debate and that this hypothesis is reevaluated according to rigorous scientific criteria. Apart from the obvious need to advance our understanding of the potential carcinogenic hazard implicit in this mechanism, there is the subsidiary question of whether an agent such as limonene is formally required to be active in the TgAC and the p53 mouse abbreviated carcinogenicity bioassays. As things stand at the moment (*2*), a positive result in both of these assays would define limonene as a genotoxic carcinogen, whereas a positive result in only the TgAC skin painting assay would define it as a nongenotoxic carcinogen. A negative result in both assays would probably be rationalized along the lines that limonene represents the type of nongenotoxic carcinogen that modern methods should not be required to detect, i.e., that it should be classified as "generally regarded as safe" (*2*). In fact, the suggested need for such abbreviated carcinogenicity bioassays of limonene would probably flow from a full analysis of the α2u-globulin hypothesis, but that, in turn, would imply that these two assays are already confirmed as giving mechanistically diagnostic data, which they are not. Thus, the importance of resolving the α2u-globulin debate.

Science proceeds by way of informed speculation. However, such speculations should not become personal property to defend at all costs. Rather, they should be vigorously challenged with the aim of either refuting them or transforming them into generally accepted facts. The sooner that happens with the speculations surrounding the α2u-globulin hypothesis, the better.

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References

1. Melnick RL, Kohn MC, Huff J. Weight of evidence versus weight of speculation to evaluate the α2u-globulin hypothesis. Environ Health Perspect 105:904–906 (1997).
2. Tennant RW, French JE, Spalding JW. Identifying chemical carcinogens and assessing potential risk in short-term bioassays using transgenic mouse models. Environ Health Perspect 103: 942–950 (1995).

Re: "A Pilot Study of Urinary Estrogen Metabolites (16α-OHE_1 and 2-OHE_1) in Postmenopausal Women with and without Breast Cancer"

Ursin et al. (*1*) report data on the absence of a difference in the 2-hydroxyestrone/16α-hydroxyestrone (2-OHE_1/16α-OHE_1) ratio between breast cancer cases and controls. These findings contrast with pilot data recently reported by Kabat et al. (*2*), indicating a strong and statistically significant inverse association of the ratio with postmenopausal breast cancer, as well as in other recently reported studies (*3*). There are a number of methodological aspects of the study by Ursin et al. (*1*) that require comment.

First, although it is not explicitly stated, the authors recontacted women who participated in an earlier case–control study of breast cancer (*4*) to obtain urine samples from those qualified survivors who agreed to participate. The cases had been diagnosed between March 1987 and December 1989 and were recontacted approximately 7 years later. In the original population-based study, 1,510 matched case–control pairs were interviewed. Only stage I and II cases were included in that study. For the urinary estrogen study, the authors estimated that 55–60% of the original participants were excluded because they were receiving chemotherapy or other medication or weighed more than 200 pounds, which might affect estrogen metabolism.